REMARKS

This Reply is responsive to the Office Action dated June 5, 2002. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

I. Status of the Claims

Claims 1-65 were pending in this application at the time of the Office Action dated June 5, 2002. As a result of this amendment, claims 22-49, 53, 54, 60 and 61 have been canceled. Accordingly, claims 1-21, 50-52, 55-59 and 62-65 are now pending and under examination.

II. Amendments to the Claims

Claims 1, 52 and 59 were amended above to indicate that the recited Flp transgene is a Flp "recombinase" transgene, as suggested in the Office Action at page 5. Claim 1 was also amended to indicate that the Flp recombinase transgene is expressed from a tissue-specific promoter. Support for this amendment may be found at the very least in the paragraph bridging pages 15-16, and in original claim 20. Claim 20 has been amended accordingly to delete reference to tissue type regulation, since this limitation has been incorporated into claim 1. Support for amended claim 20 whereby further means of regulation are imposed on Flp transgene expression may be found at page 16, line 2.

Claim 51 was amended to clarify that the claim is limited to genes controlling differentiation of a cell or development of an organism, in contrast to claim 15, which is not so limited.

Claims 52 and 59 were amended to incorporate the limitations of claims 53 and 54, and claims 60 and 61, respectively. Accordingly, claims 53, 54, 60 and 61 were canceled, and claims 55-57 and 62-64 were amended so as not to depend on a canceled claim.

No prohibited new matter was added by any of these amendments.

III. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 2-60 and 62-65 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a FLP recombinase transgene under the control of a tissue-specific promoter and the reporter gene under control of a non-tissue-specific promoter wherein the reporter gene comprises a disruption of two FLP recognition sequences in direct repeat orientation such that the reporter gene produces active product only when in the recombined form, allegedly fails to provide enablement for transgenic mice as broadly as claimed.

Claim 1 was separately rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabled for a transgenic mouse comprising an FLP recombinase transgene under the control of a tissue-specific promoter, allegedly fails to provide enablement for transgenic mice having the FLP transgene under control of any type of promoter as broadly as claimed. According to both rejections, the claims "must

be congruent with the asserted utility of the invention, which in the instant case is cell fate mapping."

Without agreeing with the rejections, Applicants have limited claim 1 by amendment to recite a transgenic mouse comprising a FLP recombinase transgene under control of a tissue-specific promoter. Accordingly, the separate rejection of claim 1 under §112, first paragraph is now moot and should be withdrawn. Claim 20 has been amended to delete reference to tissue type regulation in view of the amendment to claim 1.

The reasoning behind the separate rejection of claims 2-60 and 62-65 is unclear, but it appears the amendment to claim 1 should resolve the rejection at least as it pertains to claims 2-21 and 50-51, since these claims are either directly or indirectly dependent on claim 1 and are therefore more narrow in scope than amended claim 1. If amended claim 1 is enabled as to its full scope, then dependent claims that are more narrow should also be enabled. Claims 22-49 have been canceled in order to expedite an allowance of the other claims, but such cancellation should be understood to be without prejudice to future prosecution in a continuation application. Indeed, in contrast to the rationale offered for the rejections under §112, first paragraph, the specification is not limited to the utility of cell fate mapping (see, for instance, pages 4-7, discussing the embodiments of making mutations in specific cells and/or at specific developmental stages, site specific integration of transgenes to minimize confounding effects on chromatin structure, and models for studying carcinogenesis).

Claim 61 was excluded from the rejection under §112, first paragraph. Accordingly, without agreeing with the rejection and solely in the interest of expediting

an allowance of this application, the limitations of claim 61, and claim 60 on which it depends, were incorporated into the base claim, claim 59. Claims 60 and 61 were therefore canceled. Since claim 59 now incorporates the limitations of claims 60 and 61, and claim 61 was not rejected for lack of enablement, amended claim 59 should be free of the rejection under §112, first paragraph. In addition, the rejection should also be withdrawn as to claims 62-65, which are dependent on, and therefore more narrow, than claim 59. Applicants reserve the right to prosecute the canceled subject matter in a continuation application, because clearly, recombination mediated by the Flp transgene may be detected by other means than gene activation (for instance, by inactivation of the second transgene, as disclosed at page 20, lines 19-20).

Although claim 54 was not excluded from the rejection, it appears that this claim should also be free of the enablement rejection because it is a transgenic mouse claim that has parallel limitations to the method claim of enabled claim 61. Accordingly, in the interest of expediting an allowance of this application, the limitations of claim 54, and claim 53 on which it depends, were incorporated into the base claim, claim 52. Claims 53 and 54 were therefore canceled. In view of the similar limitations of claims 54 and 61, and the amendment of claim 52 to incorporate the limitations of claim 54, the rejection of claim 52 (and claims 55-58 that are dependent thereon) should now be withdrawn.

In view of the amendments and remarks above, withdrawal of the rejections under 35 U.S.C. §112, first paragraph, of remaining claims 1-21, 50-52, 55-59 and 62-65 are respectfully requested.

IV. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 54 and 61 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way so as to reasonably convey that the inventors had possession of the claimed invention. In particular, the Examiner has asked that Applicants point to specific support in the specification for the term "ubiquitous promoter." In response, Applicants respectfully note that support for the recited phrase may be found in the specification in the first paragraph of page 17.

V. Rejections under 35 U.S.C. §112, second paragraph

Claims 1-65 were rejected under §112, second paragraph, for alleged indefiniteness. Specifically, the Office Action suggests that the phrase "Flp transgene" be amended to recite "Flp recombinase transgene." Applicants have adopted this suggestion and have amended claims 1, 52 and 59 accordingly.

Claim 1 was also rejected because of the phrase "of the cell," and it was suggested that this phrase be removed. Applicants have adopted this suggestion, and further appreciate the indication that claim 1 would be allowable if this phrase was deleted and the phrase "Flp transgene" was amended to "Flp recombinase transgene."

Claim 51 was rejected because it was unclear if claim 51 should still include all the members of the Markush group of claim 15, or whether it should be limited to genes controlling differentiation of a cell or development of an organism. Applicants believe that the amendment to claim 51 entered above obviates this rejection.

Finally, claim 51 was rejected because the metes and bounds of "metabolic enzymes" and "growth/differentiation factors and their receptors" are unclear. Applicants respectfully note that gene products constituting metabolic enzymes and gene products constituting growth or differentiation factors and their receptors were well known at the time the present application was filed and would be immediately recognized by a person of skill in the art.

For instance, according to the 2nd edition of Biology, The Science of Life (1981) (eds. Wallace *et al.*), a metabolic pathway is a chain of enzymatic reactions, where the product of one enzyme becomes the substrate of the next, and so on (see page 132, attached). Further, according to the Glossary, "metabolism" is defined as the chemical changes and processes of living cells, including but not limited to respiration, the synthesis of biochemicals, and the breakdown of wastes (see page 1160, attached). Thus, it would be clear to the skilled artisan that a "metabolic enzyme" would include any cellular enzyme involved in a metabolic process of the cell, including those enzymes involved in well known metabolic pathways such as respiration and the synthesis or breakdown of cellular biochemicals.

According to Fundamental Immunology (1989) (eds. Coleman *et al.*), cells and tissues regulate their own population size by the action of "growth factors" such as nerve growth factor, epidermal growth factor, platelet-derived growth factor, and hormones such as erythropoietin (see pages 436-37, attached). There are also growth suppressing hormones, such as mitosis-suppressing hormone. And some substances, such as transforming growth factor-β, can act as either positive or negative growth regulators (see page 437). Thus, at the time the application for the present invention was filed, the

skilled artisan would have known that the term "growth factors" includes a variety of known proteins and hormones that control the growth of cells.

Finally, according to Wallace *et al.*, "differentiation" is defined as the process in development whereby a cell becomes morphologically, developmentally, or physiologically specialized (see page 1146). The authors provide an example of positive and negative differentiation factors in the sprouting factor and antisprouting factor, which are "hormone-like" substances that regulate the sprouting of neurones in neuronal development (see page 981). Hence, given the exemplary disclosure of Wallace *et al.*, which was published in 1981, it would have been clear to the skilled artisan at the time the present application was filed that a differentiation factor is any hormone-like protein that positively or negatively regulates or affects the morphological, developmental or physiological differentiation of a cell.

In view of the amendments and remarks above, reconsideration and withdrawal of the rejections under §112, second paragraph are respectfully requested.

This reply is fully responsive to the Office Action dated June 5, 2002. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted
Morgan, Lewis & Bockius LLP

Dated: **December 4, 2002**
Morgan, Lewis & Bockius LLP
Customer No. 09629
1111 Pennsylvania Avenue, NW
Washington, D.C. 20004
202-739-3000
202-739-3001

Bonnie Weiss McLeod
Registration No. 43,255

APPENDIX

The following amendments were entered above:

IN THE CLAIMS

Claims 22-49, 53, 54, 60 and 61 were canceled.

The following claims were amended as indicated:

1. (Amended) A transgenic mouse comprising a Flp recombinase transgene under control of a tissue-specific promoter integrated in a genome of the transgenic mouse, wherein the Flp recombinase transgene is expressed in a cell of the transgenic mouse at a level of recombinase activity sufficient to catalyze recombination between Flp-recognition sequences [of the cell].

20. (Amended) The transgenic mouse according to Claim 1, wherein Flp recombinase activity is further regulated by a factor selected from the group consisting of chemical, developmental stage and temperature[, and tissue type].

51. (Twice Amended) The transgenic mouse according to claim 15, wherein said [genes] another transgene is a gene controlling differentiation of a cell or development of an organism [are] selected from the group consisting of genes encoding adhesion molecules, cyclin kinase inhibitors, Wnt family members, Pax family members, Winged helix family members, Hox family members, cytokines, interleukins, growth/differentiation factors and their receptors, kinases, phosphatases, metabolic enzymes, and antigen receptors.

52. (Amended) A transgenic mouse comprising [an] a Flp recombinase transgene intergrated into the genome of the transgenic mouse, wherein the Flp recombinase transgene is expressed from a tissue specific or a developmental stage specific promoter in at least one cell of the transgenic mouse at a level sufficient to catalyze recombination between two FLP-recognition sequences in direct repeat orientation in said cell, wherein said recombination is detected by activation of a gene expressed from a ubiquitous promoter, wherein said gene produces a detectable product only when in recombined form.

55. (Amended) The transgenic mouse of claim [53] 52, wherein said detectable product is a histochemical marker encoded by said gene selected from the group consisting of alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase, luciferase, green fluorescent protein and β-glucuronidase.

56. (Amended) The transgenic mouse of claim [53] 52, wherein said detectable product is a transcript expressed from said gene in recombined form that is detectable by *in situ* hybridization.

57. (Amended) The transgenic mouse of claim [53] 52, wherein said detectable product is a peptide tag encoded by said gene that is detectable by binding to a cognate binder.

59. (Amended) A method of mapping the developmental fate of a cell *in vivo* comprising:

(d) providing a transgenic mouse comprising a genome which contains a Flp recombinase transgene under control of a tissue-specific or developmental stage specific promoter and at least two FLP recognition sequences in direct orientation;

(e) expressing the Flp recombinase transgene at a level sufficient to catalyze site-specific recombination between said FLP recognition sequences in at least one cell; and

(f) detecting said recombination in said at least one cell by detecting activation of a gene expressed from a ubiquitous promoter, wherein said gene produces a detectable product only when in recombined form, and wherein said recombination is evidence of expression of said Flp transgene in said cell or a developmental precursor to said cell.

62. (Amended) The method of claim [60] 59, wherein said detectable product is a histochemical marker encoded by said gene selected from the group consisting of alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase, luciferase, green fluorescent protein and β-glucuronidase.

63. (Amended) The method of claim [60] 59, wherein said detectable product is a transcript expressed from said gene in recombined form that is detectable by *in situ* hybridization.

64. (Amended) The method of claim [60] 59, wherein said detectable product is a peptide tag encoded by said gene that is detectable by binding to a cognate binder.